REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary indicates that claims 21-40 are pending in the application. However, the Detailed Action clearly states that claim 38 is subject to a restriction requirement. Claim 38 is withdrawn from consideration. Claims 21-37, 39 and 40 are under consideration and stand rejected.

Claims 21-22, 29-30, 39 and 40 have been amended.

Claim 21 has been amended to more thoroughly describe the claimed subject matter by further characterizing the modification to the polypeptide encoded by the vector of the invention, and to better conform the claim to U.S. practice and grammar. Support for the amendments to claim 21 can be found in the specification in at least the paragraph bridging pages 3-4, at page 6, lines 3-12, and the claims as originally filed.

Claim 22 has been amended to more clearly describe the claimed subject matter. Support for the amendments to claim 22 can be found in the specification in at least the claims as filed.

Claim 24 has been amended to recite the term "genome" as suggested by the Examiner. Support for the amendment may be found in at least the original claims.

Claim 30 has been amended to delete alternative subject matter which is now the subject of new claim 43. Support for the amendment may be found at least in the claims as originally filed.

Claim 39 was amended in the preamble to refer specifically to the treatment aspect claimed method. Support for the amendment may be found throughout the specification and at least in the claims as originally filed.

Claim 40 has been amended to more clearly describe the invention. Support for the amendment may be found at least in the claims as originally filed.

New Claims 41-64 are added for examination.

New Claims 41 and 42 recite the preventative aspect canceled from Claims 39-40. Support for Claim 41 may be found in the claims as originally filed.

New Claim 43 recites the subject matter canceled from Claim 30.

New independent Claim 44 recites a composition as described in Claim 21 wherein the vector and polypeptide are further characterized. Support for Claim 44 may be found at least in the original claims and at page 6, lines 3-12, page 7, line 33 to page 8, line 9, page 14, lines 31-32, previous Claim 26 and Examples 1 and 2.

New Claims 45-64 recite features of embodiments of the composition of Claim 44, the vector and a viral particle of the composition, and methods for using the composition. Support for Claims 45-64 derive from throughout the specification and the original claims.

New Claim 60 recites an embodiment of the invention wherein the polypeptide described in Claim 44 is a non-oncogenic mutant of the E6 polypeptide having a specific deletion. Further support for new Claim 60 may be found at least at page 32, lines 4-7.

New Claim 61 recites an embodiment of the invention wherein the polypeptide described in Claim 44 is a non-oncogenic mutant of the E7 polypeptide having a specific deletion. Further support for new Claim 60 may be found at least at page 31, lines 5-7.

New Claim 61 recites an embodiment of the invention wherein the polypeptide described in Claim 44 is a non-oncogenic mutant of the E7 polypeptide having a specific deletion. Further support for new Claim 61 may be found at least at page 31, lines 5-7.

The Official Action provides a reminder of the proper language and format for an abstract of the disclosure. This Response includes an Abstract which is believed to be descriptive of the claimed invention.

No prohibited new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of the present Amendments.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 22 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because it is purportedly unclear whether the polypeptide has a nuclear localization sequence. Claim 22 has been amended to better conform to U.S. grammatical usage. Claim 22, as amended, describes an embodiment of the composition of the

invention wherein the polypeptide described in Claim 21 has a nuclear location in its natural form, however the natural nuclear localization sequence is deleted. From Claim 21, as amended, it is clear that the polypeptide is also modified by inserting a membrane anchoring sequence so as to have a membrane location at the surface of the cells in which it is expressed. Claim 22, as amended, can be clearly understood by one of skill in the art. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. By the present amendment, claim 24 has been amended in accordance with the Examiner's suggestion. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 40 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the claim purportedly refers to a cancer or tumor as including conditions which are not necessarily a cancer or tumor. Claim 40 as amended describes an embodiment of the method of claim 39 wherein the subject is diagnosed with a condition consistent with the presence or imminence of cancer or a tumor. Claim 40, as amended, can be clearly understood by one of skill in the art. Accordingly, withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 21-37, 39 and 40 stand rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable one of skill in the art to use the

invention commensurate with the scope of the claims. The Official Action acknowledges that the specification is enabling for treatment of cancer or a tumor in a subject by subcutaneous, intraperitoneal, intramuscular, or scarification delivery of a vaccinia vector encoding the HPV E6 or E7 proteins. The Official Action also acknowledges prevention of cancer or a tumor in a mouse model.

The Official Action alleges that neither the specification or the state of the art reasonably provides enablement for the use of all vector systems, all routes of administration, for this invention to prevent cancer in any subject, or for the use of any mutated forms of E6 and E7 proteins. It is up to the Examiner to supply substantive reasons to doubt why the presently claimed invention can not be used as disclosed in the specification. Only when "the examiner's basis for questioning the sufficiency of the disclosure is reasonable [does] the burden shifts to appellants to come forward with evidence to rebut this challenge." *Ex parte Dash*, 27 USPQ2d 1481, 1484 (BPAI 1993). "When rejecting a claim under the enablement requirement of section 112, the PTO bears the initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling." *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)(with emphasis).

Although Applicants understand that Examiners are frequently knowledgeable in the art pertaining to the patent applications which they examine, a mere allegation that the specification does not enable a claimed embodiment is not sufficient given the persuasive *in vivo* examples presented in the specification. According to the Federal Circuit, an allegation needs to be sufficiently supported before the burden shifts to Applicants. The Examiner has not met his burden in the outstanding Official Action. The Examiner has not presented substantive reasons to doubt that the presently claimed invention may be used as disclosed with any appropriate route of administration contemplated in the specification or recognized in the art, with any appropriate vector system contemplated in the specification or recognized in the art, or that the improved immunity and therapeutic efficacy could not be achieved with a vector encoding any immunogenic polypeptide modified to have a membrane location at the surface of the cells in which it is expressed.

The Office Action cites McCluskie et al. (*Molecular Medicine*, 5:287-300, 1999) on page 5 suggesting that results in mice are not perfectly predictive of human efficacy. Apparently on the basis of this citation alone, the Examiner asserts, on page 7, that "it is not apparent how one skilled in the art reasonably extrapolates, without undue experimentation, from the mouse model to the full scope of the claimed invention." Such a standard, if actually upheld by the Office, would render it nearly impossible for those working in the pharmaceutical industry to ever obtain valid patents. For this reason, the Federal Circuit has cautioned the PTO not to "confuse[] the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a

particular drug for human consumption." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). The Federal Circuit also stressed that precedential authority "has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *Id.* "FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were [the PTO] to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." *Id.* at 1442-43. Thus, it is sufficient to show that a therapeutic or prophylactic immune response may be achieved in an appropriate animal model.

It is important to note that Claims 21-37 are directed to compositions, and as such, only one valid use need be disclosed and enabled for the claimed compositions to satisfy the requirements of 35 U.S.C. §112, first paragraph. "The how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. §101 that the specification disclose as a matter of fact a practical utility for the invention." *In re Ziegler*, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993). "When a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown." *Raytheon Company v. Roper Corporation*,

220 USPQ 592, 598 (Fed Cir 1983); *Cross v. Iuzuka*, 224 USPQ 739, 743 (Fed. Cir. 1985) (with emphasis).

Thus, with respect to the claimed compositions, the specification demonstrates that the claimed compositions have utility in treating and protecting against and malignant tumors *in vivo*. Moreover, as pharmaceutical compositions, they may be used in conjunction with other known treatments to provide a synergistic or even additive effect. Therefore, the Examiner's emphasis on the predictability of vaccines "fully preventing cancer in any subject" is not appropriate in the context of these claims. Indeed, the induction of an immune response is all that need be accomplished for a valid use for the claimed compositions to be enabled, and Applicants have demonstrated the ability of the claimed antigen to elicit such an immune response. Claims 21-37 are therefore fully enabled.

To support the rejection, on pages 5 and 6, the Official Action cites a number of tangentially related scientific publications that discuss various challenges associated with the field of gene therapy. The Official Action does not reveal how any of these citations proves that the invention as claimed is not enabled. The challenges described in these publications do not impact the enablement of the present application. The present invention is not intended for the treatment of disorders requiring the long term correction of a gene defect. Rather, the present invention is intended to induce immune response to viral/tumor antigens involved in tumor establishment or development. This goal may be achieved by transient expression of an appropriate immunogen. Challenges such as tissue specificity

and long term gene expression stability are not key factors in the enablement of the present invention. Therefore, neither Miller's nor Deonarain's description of developing targeting strategies in the field of gene therapy is relevant to the present invention. Likewise, Verma's review of vector targeting and long-term expression issues is not relevant. On the other hand, Crystal (*Science*, 270:404-410, 1995; cited by the Examiner) clearly states on page 405, column 3, that "**most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo* and that all vector types function as intended.**" Crystal supports this statement with **Tables 1 and 2 which list many examples of successful gene transfer and experiments demonstrating a biologic response that is relevant to the underlying disease**. Crystal expresses hopes for continued progress in the field of long term correction of genetic defects. However, **Crystal does not provide any evidence that the presently claimed invention is not enabled.** None of the references cited in the Official Action provide substantive relevant evidence that would lead one of skill in the art to doubt that invention disclosed in the specification can be made and used in accordance with the scope of the currently pending claims.

Vector Systems

The Official Action alleges that neither the specification or the state of the art reasonably provides enablement for the use of all vector systems. The Examiner has not provided any substantive reason to doubt that one of skill in the art could not make and use the presently claimed invention using any vector system disclosed by the specification or

recognized in the art. Therefore, Applicants are under no burden to rebut the rejection. Nevertheless, this allegation is respectfully traversed.

The specification provides guidance for the use of a number of vectors including poxvirus and adenovirus vectors. A number of other vectors have been recognized and used in the field. As discussed below, there is substantial evidence that one of skill in the art could use any vector contemplated in the specification or recognized in the art in accordance with the invention as described in the specification.

For example, Taylor et al., *Virology,* 187:321-8, 1992; (attached hereto as Exhibit A) mentions that two members of the poxvirus family other than vaccinia virus have been developed as live virus vectors. Fowlpox and canarypox vectors were shown to elicit broad immunity against various pathogens. While these viruses are not capable of productive viral replication in mammalian cells, it has been demonstrated that recombinant avipoxviruses innoculated into non-avian cells authentically express foreign genes. Moreover, as demonstrated in experiments in mice, cats, and dogs, the level of immunity and protection against a lethal virus challenge was at lest equivalent to those obtained with conventional vaccinia viruses expressing the same foreign immunogens (see pages 321 and 326). Moreover, Carol and Moss, *Current Opinion in Biotechnology*, 8:573-7 (1997) (attached hereto as Exhibit B) confirms that **the basic technology of vaccinia virus may be used for all members of the poxvirus family** (see page 574).

Likewise, adenoviruses expressing foreign antigens have been used successfully in immunization experiments. Indeed, the use of adenovirus for expressing foreign genes has

been well established for some time. For example, adenovirus expressing p53 has reached phase III clinical trials. A recent review by Kay et al. (*Nature Medicine*, 7:33-40, 2001; attached hereto as Exhibit C) refers to published reports spanning 1997-2000 when reporting:

> [M]ore recently, [adenoviruses] have been primarily used in clinical trials for the treatment of cancer in part because of their efficiency of gene transfer but also because cellular toxicity and immunogenicity may actually enhance the anti-tumor effects with specific approaches that are ongoing. (See page 36, last full paragraph.)

One of skill in the art is aware of these and other studies which establish the usefulness of numerous suitable vectors. These examples demonstrate that one of skill in the art would know how to use any appropriate vector in accordance with the presently claimed invention. (See also, Crystal (*Science*, 270:404-410, 1995) at page 405, column 3, quoted above.)

Certainly, in view of the forgoing, one skilled in the art would know how to use at least the genus of non-integrative vectors, exemplified by poxviruses and adenoviruses, to make and use anti-tumoral compositions in accordance with the invention. New Claim 44 describes the vector of the presently claimed composition as a non-integrative vector which is supported in the specification at least at page 14, lines 27-35. As clearly demonstrated by the specification and the state of the art, one of skill in the art could make and use the composition of Claim 44 using any non-integrative vector.

Routes of Administration

The Official Action alleges that neither the specification or the state of the art reasonably provides enablement for the use of all routes of administration. The Examiner has not provided any substantive reasons to doubt that the specification is enabling for the use of any mode of administration. Therefore, Applicants are under no burden to rebut the allegation. Nevertheless, as set forth below, this allegation is respectfully traversed.

The working examples disclosed in the present application demonstrate anti-tumoral protection following administration of a vaccinia virus-based composition when administered via four standard routes. Specifically, scarification, subcutaneous, intraperitoneal, and intramuscular injection are exemplified. The specification also discloses additional exemplary modes of administration which are standard in the art such as intravenous, intratumoral, and subepithelial injections.

Prior to the present invention, the use of engineered virus vectors to express polypeptides or peptide epitopes was a well known technique. As described by Gluck and Kieny in *Vaccines and Immunotherapy*, pp. 246-53 (Cryz, S.J. Jr., Ed., 1991, Pergamon Press, New York; (attached hereto as Exhibit D) experimental animals immunized with a vaccinia virus expressing an antigenic polypeptide via several different routes of administration are protected against subsequent challenge. For example, intradermal inoculation of rabbits and mice resulted in a rapid induction of rabies virus neutralizing antibodies (see page 252). Induction of rabies neutralizing antibodies was observed

irrespective of the route of inoculation: intramuscular, intradermal, and oral routes were all effective (see page 253).

As another example, Acres et al. (*Therapeutic Immunology*, 1:17-23, 1994; attached hereto as Exhibit E) provide experimental evidence that intravenous administered recombinant vaccinia viruses predominantly reach tumor cells implanted in an animal. Tumor-bearing mice were intravenously injected with recombinant or control vaccinia virus. A substantial majority of the viral particles were detected in tumor cells whereas most internal organs had little or no detectable vaccinia virus. In view of the above, one of skill in the art would expect any recognized mode of administration to be effective.

The specification demonstrates the effectiveness of four example modes of administration and provides guidance as to other example modes which are known in the art. The state of the art recognizes the effectiveness of these and other methods. Based on the present disclosure and the state of the art, one of skill in the art would have no reason to doubt the effectiveness of any recognized mode of administration for use with the composition of the present invention. Therefore, the specification and the state of the art do provide enablement for effective administration of the composition of the invention by any route of administration without undue experimentation.

Tumor Antigens

The Official Action alleges that the specification does not provide enablement for the use of all mutated forms of E6 and E7 proteins. It is up to the Examiner to supply substantive reasons to doubt why vectors encoding any mutated forms of E6 and E7

proteins modified according to the presently claimed invention can not be used as disclosed in the specification. In the present Official Action, no reasons **at all** are given for the allegation that "the specification does not enable the use of all mutated forms of E6 and E7 proteins." The Examiner provides no rational for his distinction that only polypeptides derived from non-oncogenic forms of the E6 and E7 proteins are enabled. As stated above, applicants have no burden to rebut such an unsupported allegation of lack of enablement. Nevertheless, this allegation is respectfully traversed.

The improved antitumoral immunity and therapy provided by the present invention can be achieved with a composition comprising a vector encoding any suitable immunogenic polypeptide modified to have surface membrane location. The working examples of the application provide experimental evidence that modifying HPV-16 E6 and E7 tumor antigens to locate on the cell membrane surface improves antitumor immunity and therapeutic benefits. Specifically, the Examples prove that compositions comprising vaccinia vectors encoding non-oncogenic mutants of the E6 and E7 HPV antigens in a membrane anchored form is more effective than a counterpart expressing intracellular E6 and E7 antigens. The difference in activity can be attributed to the membrane location at the surface of the cells in which it is expressed.

The application presents experiments using non-oncogenic mutants as **examples**. However, numerous immunization experiments in the literature have established that mutated as well as native E6 and E7 HPV polypeptides are capable of evoking a protective response in humans or animals. Indeed, successful vaccination was obtained following

administration of non-mutated HPV early polypeptides as well as their non oncogenic variants. See, for example, Jarrett et al. (*Virology*, 184:33-42, 1991; cited by the Examiner) which discusses animal vaccination conducted with native E6 and E7 papillomavirus antigens. Jarrett et al., state that "calves vaccinated with BPV-4 E7 undergo early rejection of alimentary canal papillomas. Immunization of rats with recombinant vaccinia viruses expressing the E6 and E7 protein of HPV-16 retarded or prevented the development of tumors induced by HPV-16 transformed cells. Therefore, the early proteins too appear to be involved in eliciting an immune response against tumors" (See page 41, second column). Boursnell et al. (*Vaccine*, 14:1485-94, 1996; cited by the Examiner) also reported successful vaccination following administration of a vaccinia virus expressing intracellular mutants of E6 and E7 proteins (fused E6 and E7 antigens from HPV-16 and HPV-18 in which the native E7 antigens are mutated). These examples, taken with the working examples of the present specification, demonstrate that both native and mutant viral antigens are capable of eliciting efficient immune response in injected hosts.

Thus, an established and growing body of evidence indicates that native E6 and E7 antigens as well as mutated non-oncogenic E6 and E7 antigens can act to elicit a beneficial immune response. The present application discloses that any such antigen may be modified to effect a surface membrane presentation to provide improved immunogenic potential and thus improve antitumor therapeutic and prophylactic capabilities.

No substantive reasons are presented to doubt that the present invention may be used in accordance with the full scope of the claims. Therefore, the specification must be considered to provide sufficient enablement of the claims. New Claim 44 describes an embodiment of the invention wherein an immunogenic polypeptide of the invention is encoded by the E6 or E7 region of a papillomavirus. Certainly, in view of the forgoing, the invention is at least enabled for the use of a composition comprising a vector encoding any polypeptide modified according to the invention and derived from a polypeptide encoded by the E6 or E7 region of the papillomavirus.

Prevention and Treatment of Cancer or a Tumor

Turning specifically to the method claims, the Official Action acknowledges that the specification is enabling for treatment of cancer or a tumor in a subject by subcutaneous, intraperitoneal, intramuscular, or scarification delivery of a vaccinia vector encoding the HPV E6 or E7 proteins. The Official Action also acknowledges that the specification is ennobling for the prevention of tumors in the mouse model. By the present amendment, treatment and prophylaxis aspects of the invention are now recited in separate claims. Claims 39 and 40, as amended, now refer particularly to treatment of cancer or a tumor using the composition of Claim 21.

New Claims 41 and 42 are drawn to immunoprophylaxy of cancer or a tumor using the composition of Claim 21. New Claims 58 and 59 are drawn to treatment of cancer or a tumor using the composition of Claim 44. The Official Action acknowledges that the

specification is enabling for the prevention of tumors in the mouse model. This is all that is required to support a claimed method of immunoprophylaxy.

With regard to tumor naive subjects, the Examiner has presented no substantive evidence beyond the Examiner's personal speculation, to support the implied assertion that the presently claimed methods may not be used by one of skill in the art to provide a prophylactic benefit. New Claims 41 and 42 recite the term "immunoprophylaxy" in place of "prevention" in recognition of what is well known in the art. While vaccines are commonly said to prevent disease, it is fully understood that effective and valuable vaccines may not perfectly prevent infection or disease against every challenge every time. Nevertheless, effective vaccines generally provide a prophylactic benefit to the subjects who receive them. Applicants believe that these terms as understood in the art are commonly used synonymously and that the scope of the claimed invention as to prevention is not changed.

All Claims Are Fully Enabled

For at least the reasons set forth above, the Examiner has failed to present a proper rejection under 35 U.S.C. § 112, first paragraph. Properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection. *U.S. Patent and Trademark Office 35 U.S.C. § 112 First Paragraph Training Manual, August 1996* (Citing *In re Wright* 999 F.2d 1557, 1562 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).) The Official Action recites only non-specific descriptions of tangentially related citations in the literature and broad unsupported allegations. However, as

demonstrated above, there is substantial evidence that the present invention can be made and used by one of skill in the art in accordance with the full scope of the claims. Accordingly, withdrawal of all rejections under 35 U.S.C. § 112, first paragraph are respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 21, 22, 24-26, 34-37, 39 and 40 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lin et al. (*Cancer Research*, 56:21-6 1996). Lin et al. describe a vaccinia vector expressing the HPV-16 E7 antigen modified by adding the signal peptide, and the transmembrane domain and the cytoplasmic tail of the **lysosome-associated** membrane protein (LAMP-1) at the N-terminus and C-terminus of the E7 protein. The Official Action asserts that:

> The LAMP-1 transmembrane domain is equivalent to the limitation of a membrane anchoring sequence in Claim 21 because transmembrane domain and membrane anchoring sequence are both art accepted terms that refer to a series of hydrophhobic amino acids that function to retain a protein in a cell membrane.

However, the LAMP-1 domain is distinct from the membrane anchoring sequence contemplated by the present invention. The LAMP-1 sequence targets a protein to a lysosomal/endosomal location. Claim 21, as amended, has been clarified to recite the surface membrane localization of the modified polypeptides of the present invention.

As evidenced by Wu et al. (PNAS, 92:11671-75, 1995; attached herewith as Exhibit F) cells transformed with the chimeric E7-LAMP-1 construct displayed a vesicular pattern

consistent with endosomal and lysosomal localization. (See Figure 2A, page 11673 and results discussed on page 11672.) The LAMP-1 sorting signals reroute the E7 antigen into the MHC class II processing pathway to improve the $CD4^+$-mediated immune response. This is an interesting approach to improving immune response, but is distinctly different from the presently claimed invention.

Claim 21, as amended, recites the surface membrane localization of the modified polypeptides of the present invention. One of skill in the art can immediately recognize sequences which produce a membrane localization at the cell surface such that one end is exposed to the exterior of the cell and one end is exposed to the cytosol as described in the specification at page 6 lines 3-12. Such sequences are distinct from the LAMP-1 sequence which targets an endosomal and lysosomal localization.

Therefore, Lin et al. do not anticipate the presently claimed invention. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 21, 24-27, 34-37, 39 and 40 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Lin et al. in view of Boursnell et al. (*Vaccine*, 14:1485-94, 1996). As discussed above, Lin et al. teach a vaccinia vector expressing a HPV E7 polypeptide which is modified to target the lysosomes and endosomes. Lin et al. do not teach or suggest any polypeptide modified to have a membrane localization at the surface of

the cells in which the polypeptide is expressed. Boursnell et al. teach non-oncogenic E7 mutants that eliminate Rb binding. Boursnell et al. do not teach the use of a membrane anchoring sequence so as to have a membrane location at the surface of the cells in which the modified polypeptide is expressed. In fact, Boursnell et al. teach against the present invention on page 1486 in stating that antigen must be produced inside host cells. Therefore, the references may not be combined to arrive at the presently claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103 is respectfully requested.

Claims 21, 24, 28, and 29 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Lin et al. in view of Jarrett et al. (*Virology*, 184:33-42, 1991). Lin et al. do not teach or suggest any polypeptide modified to have a membrane localization at the surface of the cells in which the polypeptide is expressed. Jarrett et al. teach cattle vaccination with papillomavirus L1 and L2 proteins. Jarrett et al. do not teach the use of a membrane anchoring sequence so as to have a membrane location at the surface of the cells in which the modified polypeptide is expressed. Therefore, the references may not be combined to arrive at the presently claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103 is respectfully requested.

Claims 21 and 31-33 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Lin et al. in view of Chow et al.(*J. Virol.* 71:169-178, 1997), He et al. (*Gene*, 175:121-5 1996), Kim et al. (*J. Immunol.*, Jan 15, pp. 816-26, 1997), or Finke (*Gene Therapy*, 5, 31-9, 1998). Applicants note that Finke et al. is not prior art because it is published significantly after the priority date of the present application. Lin et al. do not

teach or suggest any polypeptide modified to have a membrane localization at the surface of the cells in which the polypeptide is expressed. As stated in the Official Action, none of Chow et al., He et al. Kim et al. nor Finke et al. teach the use of a membrane anchoring sequence. Therefore, the references may not be combined to arrive at the presently claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103 is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment dated November 5, 2001

Marked-up Claims 21, 22, 24, 30, 39 and 40

21. (Amended) An antitumoral composition comprising at least one recombinant vector [containing] comprising sequences encoding [one or more] at least one immunogenic polypeptide[(s)], wherein said polypeptide[(s)] is a polypeptide naturally having a nonmembrane location and which is modified by inserting a membrane anchoring sequence so as to have a membrane location [in] at the surface of the cells in which it is expressed.

22. (Amended) The antitumoral composition according to claim 21, wherein said polypeptide naturally has a nuclear location and [is, in addition, deleted from] wherein its natural nuclear localization sequence is deleted.

24. (Amended) The antitumoral composition according to claim 21, wherein said immunogenic polypeptide originates from an early [and/]or late region of a papillomavirus genome.

30. (Amended) The antitumoral composition according to claim 21, wherein at least one immunogenic polypeptide is such that:

(1) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 1,

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Marked-up Claims 21, 22, 24, 30, 39 and 40

(2) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 2, or

(3) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 1 and an immunogenic polypeptide having a sequence homologous or identical to that shown in SEQ ID NO: 2[,].

[(4) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 1, an immunogenic polypeptide derived from the L1 protein of a papillomavirus and/or an immunogenic polypeptide derived from the L2 protein of a papillomavirus,

(5) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 2, an immunogenic polypeptide derived from the L1 protein of a papillomavirus and/or an immunogenic polypeptide derived from the L2 protein of a papillomavirus, or

(6) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 1, an immunogenic polypeptide having a sequence homologous or identical to that shown in SEQ ID NO: 2, an immunogenic polypeptide derived from the L1 protein of a papillomavirus and/or an immunogenic polypeptide derived from the L2 protein of a papillomavirus.]

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Marked-up Claims 21, 22, 24, 30, 39 and 40

39. (Amended) A method for the treatment [or prevention] of cancer or a tumor in a subject comprising administering an effective amount of the antitumoral composition of claim 21 to said subject to treat or prevent said cancer or tumor in said subject.

40. (Amended) The method of claim 39, wherein said [cancer or tumor is] subject is diagnosed as having a cancer of the cervix, a low-grade cervical dysplasia or a papillomavirus infection.